

Application Serial No. 10/627,685
Amendment Dated 13 January 2005
Reply to Office Action of 13 July 2004

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (original): A method for treating disorders associated with radical depolarization of excitable membranes by activating a K_{ATP} channel which comprises administering to an individual in need thereof an effective amount of an active agent selected from the group consisting of:

(a) a compound of the following formula

Cys-Xaa₁-Ile-Xaa₂-Asn-Gln-Xaa₃-Cys-Xaa₄-Gln-Xaa₅-Leu-Asp-Asp-Cys-Cys-Ser-Xaa₁-Xaa₃-Cys-Asn-Xaa₁-Xaa₄-Asn-Xaa₃-Cys-Val (SEQ ID NO:1), wherein Xaa₁ and Xaa₃ are independently Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N'-trimethyl-Lys, any synthetic basic amino acid, His or halo-His; Xaa₂ is Pro or hydroxy-Pro (Hyp); Xaa₄ is Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or any synthetic aromatic amino acid; and Xaa₅ is His or halo-His,

(b) an analog of the compound of (a), said analog selected from the group consisting of:

κ-PVIIA[R18A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Ala-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:2);

κ-PVIIA[R22A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Ala-Phe-Asn-Lys-Cys-Val (SEQ ID NO:3);

κ-PVIIA[I3A]: Cys-Arg-Ala-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:4);

κ-PVIIA[K19A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Ala-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:5);

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κ-PVIIA[R2A]: Cys-Ala-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:6);

κ-PVIIA[F9A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Ala-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:7);

κ-PVIIA[K25A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Ala-Cys-Val (SEQ ID NO:8);

κ-PVIIA[R2K]: Cys-Lys-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:9);

κ-PVIIA[K7A]: Cys-Arg-Ile-Hyp-Asn-Gln-Ala-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:10);

κ-PVIIA[F9M]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Met-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:11);

κ-PVIIA[F9Y]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Tyr-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:12);

κ-PVIIA[R2Q]: Cys-Gln-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:13);

κ-PVIIA[H11A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-Ala-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:14);

κ-PVIIA[D14A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Ala-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:15);

κ-PVIIA[Q6A]: Cys-Arg-Ile-Hyp-Asn-Ala-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:16);

κ-PVIIA[N21A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Ala-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:17);

κ-PVIIA[S17A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ala-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:18);

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κ -PVIIA[N24A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Ala-Lys-Cys-Val (SEQ ID NO:19);

κ -PVIIA[L12A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Ala-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:20);

κ -PVIIA[D13A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Ala-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:21);

κ -PVIIA[Q10A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Ala-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:22);

κ -PVIIA[V27A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Ala (SEQ ID NO:23);

κ -PVIIA[O4A]: Cys-Arg-Ile-Ala-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:24); and

κ -PVIIA[N5A]: Cys-Arg-Ile-Hyp-Ala-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:25);

(c) a derivative of (a) or (b); and

(d) a physiologically acceptable salt thereof.

Claim 2 (original): The method of claim 1, wherein Xaa₂ is hydroxy-Pro.

Claim 3 (original): The method of claim 1, wherein Xaa₁ is Arg, Xaa₃ is Lys, Xaa₄ is Phe and Xaa₅ is His.

Claim 4 (original): The method of claim 3, wherein Xaa₂ is hydroxy-Pro.

Claim 5 (original): The method of claim 1, wherein said disorder is cardiac ischemia.

Claim 6 (original): The method of claim 1, wherein said disorder is cerebral ischemia.

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Claim 7 (original): The method of claim 1, wherein said disorder is asthma.

Claim 8 (original): The method of claim 1, wherein said disorder is ocular ischemia.

Claim 9 (original): The method of claim 1, wherein the derivative is peptide of (a) or (b) in which the Arg residues may be substituted by Lys, ornithine, homoarginine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe and Trp residues may be substituted with any synthetic aromatic amino acid; the Asn, Ser, Thr or Hyp residues may be glycosylated (contain an N-glycan or an O-glycan); the Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L); the Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives; the acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala; the aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8; and pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp) or Cys/Ala combinations.

Claim 10 (original): A method for treating cardiac ischemia which comprises administering to an individual in need thereof an effective amount of an active agent selected from the group consisting of:

(a) a compound of the following formula

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Cys-Xaa₁-Ile-Xaa₂-Asn-Gln-Xaa₃-Cys-Xaa₄-Gln-Xaa₅-Leu-Asp-Asp-Cys-Cys-Ser-Xaa₁-Xaa₃-Cys-Asn-Xaa₁-Xaa₄-Asn-Xaa₃-Cys-Val (SEQ ID NO:1), wherein Xaa₁ and Xaa₃ are independently Arg, homoarginine, ornithine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any synthetic basic amino acid, His or halo-His; Xaa₂ is Pro or hydroxy-Pro (Hyp); Xaa₄ is Phe, Tyr, meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Trp (D or L), neo-Trp, halo-Trp (D or L) or any synthetic aromatic amino acid; and Xaa₅ is His or halo-His,

(b) an analog of the compound of (a), said analog selected from the group consisting of:

κ-PVIIA[R18A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Ala-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:2);

κ-PVIIA[R22A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Ala-Phe-Asn-Lys-Cys-Val (SEQ ID NO:3);

κ-PVIIA[I3A]: Cys-Arg-Ala-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:4);

κ-PVIIA[K19A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Ala-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:5);

κ-PVIIA[R2A]: Cys-Ala-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:6);

κ-PVIIA[F9A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Ala-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:7);

κ-PVIIA[K25A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Ala-Cys-Val (SEQ ID NO:8);

κ-PVIIA[R2K]: Cys-Lys-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:9);

κ-PVIIA[K7A]: Cys-Arg-Ile-Hyp-Asn-Gln-Ala-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:10);

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κ -PVIIA[F9M]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Met-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:11);

κ -PVIIA[F9Y]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Tyr-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:12);

κ -PVIIA[R2Q]: Cys-Gln-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:13);

κ -PVIIA[H11A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-Ala-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:14);

κ -PVIIA[D14A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Ala-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:15);

κ -PVIIA[Q6A]: Cys-Arg-Ile-Hyp-Asn-Ala-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:16);

κ -PVIIA[N21A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Ala-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:17);

κ -PVIIA[S17A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ala-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:18);

κ -PVIIA[N24A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Ala-Lys-Cys-Val (SEQ ID NO:19);

κ -PVIIA[L12A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Ala-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:20);

κ -PVIIA[D13A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Ala-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:21);

κ -PVIIA[Q10A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Ala-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:22);

κ -PVIIA[V27A]: Cys-Arg-Ile-Hyp-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Ala (SEQ ID NO:23);

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κ -PVIIA[O4A]: Cys-Arg-Ile-Ala-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:24); and

κ -PVIIA[N5A]: Cys-Arg-Ile-Hyp-Ala-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:25);

(c) a derivative of (a) or (b); and

(d) a physiologically acceptable salt thereof.

Claim 11 (original): The method of claim 10, wherein the size of reperfusion infarct resulting from cardiac ischemia is reduced.

Claim 12 (original): The method of claim 10, wherein Xaa₂ is hydroxy-Pro.

Claim 13 (original): The method of claim 12, wherein the size of reperfusion infarct resulting from cardiac ischemia is reduced.

Claim 14 (original): The method of claim 10, wherein Xaa₁ is Arg, Xaa₃ is Lys, Xaa₄ is Phe and Xaa₅ is His.

Claim 15 (original): The method of claim 14, wherein the size of reperfusion infarct resulting from cardiac ischemia is reduced.

Claim 16 (original): The method of claim 14, wherein Xaa₂ is hydroxy-Pro.

Claim 17 (original): The method of claim 16, wherein the size of reperfusion infarct resulting from cardiac ischemia is reduced.

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Claim 18 (original): The method of claim 10, wherein the derivative is peptide of (a) or (b) in which the Arg residues may be substituted by Lys, ornithine, homoarginine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoarginine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe and Trp residues may be substituted with any synthetic aromatic amino acid; the Asn, Ser, Thr or Hyp residues may be glycosylated (contain an N-glycan or an O-glycan); the Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L); the Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives; the acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala; the aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8; and pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp) or Cys/Ala combinations.

Claim 19 (original): The method of claim 18, wherein the size of reperfusion infarct resulting from cardiac ischemia is reduced.

Claim 20 (new): The method of claim 1, wherein the active agent is a compound of the formula Cys-Arg-Ile-Xaa-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:26), wherein Xaa is hydroxy-Pro.

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Claim 21 (new): The method of claim 10, wherein the active agent is a compound of the formula Cys-Arg-Ile-Xaa-Asn-Gln-Lys-Cys-Phe-Gln-His-Leu-Asp-Asp-Cys-Cys-Ser-Arg-Lys-Cys-Asn-Arg-Phe-Asn-Lys-Cys-Val (SEQ ID NO:26), wherein Xaa is hydroxy-Pro.